IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION OF ACCURACY OF TRANSLATION
IN LIEU OF SWORN TRANSLATION (37 C.F.R. 1.55 & 1.68)

The undersigned traslator, having an office at

c/o Patent Department, Sankyo Co., Ltd., No. 2-58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo, Japan

certifies and declares that:

(1) I am fully conversant both with the Japanese and English languages.

(2) (A) I have translated into English Japanese Patent Application Number filed .
A copy of said English translation is attached hereto.

(2) (B) I have carefully compared the attached English-language translation of Japanese Patent Application Number 55231/1981 filed April 13, 1981 , with the original Japanese-language patent application.

(3) The translation is, to the best of my knowledge, and belief, and accurate translation from the original into the English language.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the matter with which this translation is used.

(10)
p 16 same as
on in 1-36449

Date: February 18, 1983

Akio Ohno

[English Translation of Certified Copy]

PATENT OFFICE

JAPANESE GOVERNMENT

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application : April 13, 1981

Application Number : Patent Application No. 55231/1981

Applicant : Sankyo Company, Limited

September 10, 1981

Director-General, HARUKI SHIMADA

Patent Office

[Official Seal]

Certificate Serial No. 2530 2

Application for Patent (Patent Application pursuant to a proviso of Article 38 in Patent Law)

April 13, 1981

(5,400 yen)

To : Haruki Shimada, Director-General of the Patent Office

1. Title of Invention :

Cephalosporin derivatives and preparation thereof

2. Number of Inventions described in claim : 4

3. Inventor

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6. List of appended documents

(1) Specification	1 copy
(2) Drawings	None
(3) Power of Attorney	1 copy
(4) Duplicate of Application	1 copy

7. Other Inventor, Patent Applicant or Attorney in addition to the foregoing person

(1) Inventor

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Name	Isamu Igarashi

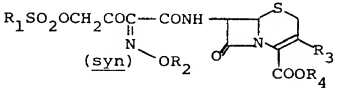
S P E C I F I C A T I O N

1. Title of the invention

Cephalosporin derivatives and preparation thereof

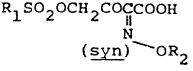
2. Scope of patent claim

(1) A cephalosporin derivative having the general formula



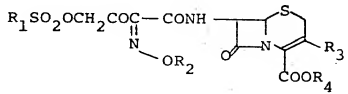
[wherein, R_1 represents an optionally substituted phenyl group, or a lower alkyl group; R_2 represents a lower alkyl group; R_3 represents a hydrogen atom, a halogen atom, a hydroxy group, a lower alkoxy group or a group of formula $-CH_2R_5$ (in which R_5 represents a hydrogen atom, a hydroxy group, a lower alkoxy group, a halogen atom, an azido group, an acyloxy group, a carbamoyloxy group or an optionally substituted heterocyclicthio group); and $COOR_4$ represents an optionally esterified carboxyl group].

(2) An alkoxyiminobutyric acid derivative having the general formula



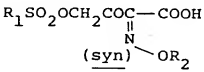
[wherein, R_1 represents an optionally substituted phenyl group, or a lower alkyl group; and R_2 represents a lower alkyl group].

(3) A process for preparing cephalosporin derivatives having the general formula



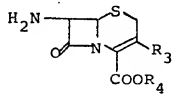
[wherein, R_1 represents an optionally substituted phenyl group, or a lower alkyl group; R_2 represents a lower alkyl group; R_3 represents a hydrogen atom, a halogen atom, a hydroxy group, a lower alkoxy group or a group of formula $-CH_2R_5$ (in which R_5 represents a hydrogen atom, a hydroxy group, a lower alkoxy group, a halogen atom, an azido group, an acyloxy group, a carbamoyloxy group or an optionally substituted heterocyclicthio group); and $COOR_4$ represents an optionally esterified carboxyl group]

which comprises reacting an alkoxyiminobutyric acid having the general formula



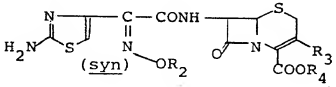
(wherein, R_1 and R_2 are as defined above)

or a reactive derivative thereof in its carboxyl group with an 7-aminocephalosporin derivative having the general formula



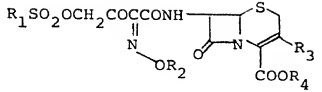
(wherein, R_3 and $COOR_4$ are as defined above).

(4) A process for preparing cephalosporin derivatives having the general formula



[wherein, R_2 represents a lower alkyl group; R_3 represents a hydrogen atom, a halogen atom, a hydroxy group, a lower alkoxy group or a group of formula $-CH_2R_5$ (in which R_5 represents a hydrogen atom, a hydroxy group, a lower alkoxy group, a halogen atom, an azido group, an acyloxy group, a carbamoyloxy group or an optionally substituted heterocyclicthio group); and $COOR_4$ represents an optionally esterified carboxyl group]

which comprises reacting a compound having the general formula

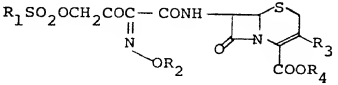


[wherein, R_1 represents an optionally substituted phenyl group, or a lower alkyl group; and R_2, R_3 and $COOR_4$ are as defined above]

with thiourea.

3. Detailed explanation of the invention

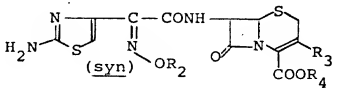
The present invention relates to cephalosporin derivatives having the general formula



(I)

[wherein, R_1 represents an optionally substituted phenyl group, or a lower alkyl group; R_2 represents a lower alkyl group; R_3 represents a hydrogen atom, a halogen atom, a hydroxy group, a lower alkoxy group or a group of formula $-CH_2R_5$ (in which R_5 represents a hydrogen atom, a hydroxy group, a lower alkoxy group, a halogen atom, an azido group, an acyloxy group, a carbamoyloxy group or an optionally substituted heterocyclicthio group); and $COOR_4$ represents an optionally esterified carboxyl group],

synthetic intermediates thereof, a process for preparing thereof, and a process for preparing 7-[2-(2-aminothiazol-4-yl)-2-(syn)alkoxyiminoacetamido]cephalosporin derivatives having the general formula



(II)

[wherein, each symbol is as defined above] characterized by reacting a compound (I) with thiourea.

Certain cephalosporins, as well as penicillins, are widely used nowadays as superior antibacterial agents for the curative and preventive purposes against infectious diseases. Yet, earnest studies are being continued for the purpose of finding out cephalosporins having the stronger antibacterial activity, broader antibacterial spectrum and/or compatibility for oral administration.

As the results among compounds represented by the abovementioned formula (II), such compounds as Cefotaxime (R_2 is a methyl group, R_3 is an acetoxymethyl group and R_4 is a hydrogen atom or sodium), Cefmenoxime (R_2 is a methyl group, R_3 is a (1-methyltetrazol-5-yl)thiomethyl group and R_4 is a hydrogen atom or sodium) and Ceftizoxime (R_2 is a methyl group, R_3 is a hydrogen atom and R_4 is a hydrogen atom or sodium) have been found out as having the stronger

antibacterial activity and the broader antibacterial spectrum and, therefore, are being practiced for the clinical trials.

Further, those in which R_2 is a lower alkyl group, R_3 is a lower alkoxymethyl group and $COOR_4$ is a group to be eliminated under physiological conditions have been found out by the present inventors as having strong antibacterial activity and useful for oral administration (Japanese Patent Application No. 136449/80).

In the meantime, several processes for preparing compounds of the series are known as described, for instance, in Tetrahedron, 34, pp 2233-2243 (1978), The Journal of Antibiotics, 34, pp 171-192 (1981) and Japanese Patents Published Unexamined Nos. 102293/77, 34795/78 and 98795/79.

They may be roughly classified into two groups: i.e. the one in which the lateral chain at 7-position or 2-(2-aminothiazol-4-yl)-2-alkoxyiminoacetyl moiety, previously prepared, is combined with the 7-aminocephalosporin moiety; and another in which the aminothiazole moiety is ultimately formed by using the reaction of α-haloketone with thiourea.

In the both cases, it is important to enable actual production on an industrial basis, and to suppress by-production of anti-form compounds which are isomers unnecessary for antibacterial activity.

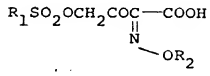
According to the studies by the present inventors, the former process turned out to produce the anti-isomer in a

considerably high yield.

The latter process is said by the literature (The Journal of Antibiotics, 34, pp 189-190) to produce the aimed product in a very low yield.

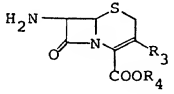
Under these circumstances, the present inventors have made studies upon industrially applicable process for preparing compounds having the aforementioned formula (II) and completed the present invention in which to obtain the aimed compounds in high yields.

Namely, the present inventors have found that the novel compounds (I) may be obtained in high yields by reacting a novel 4-sulfonyloxy-3-oxo-2-alkoxyiminobutyric acid (syn-isomer) represented by the formula (III)



(III)

(wherein the symbols are as defined above)
or a reactive derivative thereof with an 7-aminocephalosporin derivative (IV) represented by the formula



(IV)

(wherein the symbols are as defined above),
and that the compounds (II) of syn-form may be obtained in

high yields by reacting a compound (I) with thiourea.

To wit, the present invention relates to:

(1) 4-aryl(or alkyl)sulfonyloxy-3-oxo-2-alkoxyiminobutyric acids (III),

(2) 7-(4-aryl(or alkyl)sulfonyloxy-3-oxo-2-alkoxyiminobutyryl-amino)cephalosporin derivatives (I),

(3) a process for preparing compounds (I) characterized by reacting a reactive derivative of compound (III) with an 7-aminocephalosporin derivative (IV), and

(4) a process for preparing 7-[2-(2-aminothiazol-4-yl)-2-(syn)alkoxyiminoacetamido]cephalosporin derivatives characterized by reacting a compound (I) with thiourea.

In the above formulae (I) and (III), R_1 represents a lower alkyl group having from 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, n-pentyl or n-hexyl, or an optionally substituted phenyl group. The substituents, which may be the same or different and of integer of 1 - 5, include a lower alkyl group such as methyl or ethyl, a lower alkoxy group such as methoxy or ethoxy, and a halogen atom such as chlorine or bromine.

Preferably, R_1 is a phenyl, p-methylphenyl, methyl and the like.

In the above formulae (I) and (II), R_2 represents a lower alkyl group having from 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, n-pentyl

or n-hexyl, preferably methyl.

R_3 represents a hydrogen atom, a halogen atom such as chlorine or bromine, a hydroxy group, a lower alkoxy group such as methoxy or ethoxy, or an optionally substituted methyl group ($-CH_2R_5$).

The substituent R_5 includes a hydroxy group, a lower alkoxy group such as methoxy, ethoxy, n-propoxy or isopropoxy, a halogen atom such as chlorine or bromine, an azido group, an optionally substituted lower aliphatic carboxylic acid acyloxy group having 2 - 4 carbon atoms such as acetyloxy, propionyloxy or 3-oxobutyryl, a carbamoyloxy group, and a heterocyclicthio group.

The heterocyclic system here is of 5 - 6 membered ring containing 1 - 4 hetero atoms selected from O, S and N. The N atom may take the form of oxido. Such heterocyclic system includes a pyridine, N-oxypyridine, pyrimidine, pyridazine, 1,2,4-triazolone, thiazole, 1,2,3-thiadiazole, 1,3,4-thiadiazole, 1,3,4-oxadiazole, triazole, 1H-tetrazole, and the like. The heterocyclic system may be substituted with a lower alkyl group such as methyl or ethyl, a hydroxy group, a lower alkoxy group such as methoxy or ethoxy, a carboxyl group, a carbamoyl group, a carboxymethyl group, a sulfomethyl group, a dimethylaminoethyl group, and the like.

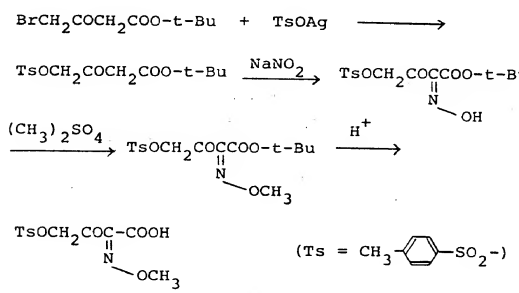
The optionally esterified carboxyl group represented by the formula $COOR_4$ means a carboxy group, its organic or

inorganic (alkali or alkaline earth metal) salts with sodium, potassium, dicyclohexylamine, etc., or an esterified carboxy group.

As such esters, there may be employed those which fill the role in protecting groups in the preparation, such as methyl, ethyl, t-butyl, benzyl, phenacyl, trimethylsilyl, benzhydryl, phenyl or methoxymethyl esters, or those which may be eliminated under physiological conditions such as phthalidyl, alkanoyloxymethyl (e.g., acetoxymethyl, propionyloxymethyl, pivaloyloxymethyl or benzoyloxymethyl), or α-ethoxycarbonyloxyethyl esters.

The reactions of the present invention will be explained hereunder.

The novel compounds (III), for example compound (IIIa) in which R_1 is a 4-methylphenyl group and R_2 is a methyl group have been prepared according to the following routes.



(IIIa)

In the reaction to obtain the compound (I) by reacting compounds (III) and (IV), the compound (III) may be used either as such or in the form of a reactive derivative. Where it is used as such, a suitable condensing agent is employed. Such condensing agent includes a disubstituted carbodiimide like N,N'-dicyclohexylcarbodiimide, an azolide compound like N,N'-carbonylimidazole, a dehydrating agent such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride or an alkoxyacetylene, and a Vilsmeyer reagent prepared from dimethylformamide and phosphorus oxychloride.

As the reactive derivative of the compound (III), there may be employed an acid halide, an acid anhydride, a mixed acid anhydride, an active ester, an active amide, an acid azide, and the like.

Such mixed acid anhydride includes those with a carbonic monoester such as monomethyl carbonate or monoisobutyl carbonate, and those with a lower alkanoic acid optionally substituted with halogen, such as pivalic acid or trichloroacetic acid.

Such active ester includes, for example, p-nitrophenyl ester, pentachlorophenyl ester, N-hydroxyphthalimide ester and N-hydroxybenzotriazole ester. Usually, the reaction is performed in a suitable solvent.

There is no limitation in the nature of the solvent as

far as it gives no adverse effect upon the reaction. Such solvent includes, for example, acetone, tetrahydrofuran, dioxane, ethyl acetate, chloroform, dichloromethane, dimethylformamide, acetonitrile and water, and mixtures of these solvents. Depending upon the variety of reactive derivative to be employed in the present reaction, there may exist a base, if necessary, in the reaction.

Such base includes, for example, an alkali metal compound such as sodium bicarbonate, potassium bicarbonate, sodium carbonate or potassium carbonate, and an aliphatic, aromatic or a nitrogen-containing heterocyclic base such as triethylamine, dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, pyridine, collidine or lutidine.

There is no special limitation as to the reaction temperature. Usually, the reaction is performed at room temperature, or under cooling.

The reaction period will vary, depending chiefly upon the variety of acylating method and reaction temperature. Usually, it is from several ten minutes to several ten hours.

Upon completion of the reaction, the compound having the formula (I) may be recovered from the reaction mixture by conventional means.

Although, it may be purified, if necessary, by recrystallization, chromatography or the like, it may also be used, without separation, for the next step.

The reaction to produce the compound (II) by reacting a compound (I) with thiourea may be performed by contacting the both reagents, usually in a suitable solvent. There is no limitation in the nature of the solvent as far as it gives no adverse effect upon the reaction. Such solvent includes, for example, water, methanol, ethanol, dimethylformamide, dimethylacetamide, acetonitrile, tetrahydrofuran, and mixtures of these solvents.

If desirable, a base such as sodium acetate or sodium bicarbonate may be added in order to promote or complete the reaction.

There is no special limitation as to the reaction temperature. Usually, the reaction is performed at room temperature.

The reaction period will vary, depending upon the reaction conditions; but it is usually from several ten minutes to several hours.

Upon completion of the reaction, the compound (II) may be recovered by conventional means.

For example, it may be isolated by concentration under reduced pressure, extraction, reprecipitation or chromatography.

Compounds (I) obtained by the process of the invention will be illustrated as follows, in which they all take the syn-form.

(1) 7-(4-p-Toluenesulfonyloxy-3-oxo-2-methoxyiminobutyryl-amino)-3-cephem-4-carboxylic acid

(2) 7-(4-p-Toluenesulfonyloxy-3-oxo-2-methoxyiminobutyryl-amino)-3-methyl-3-cephem-4-carboxylic acid

(3) 7-(4-p-Toluenesulfonyloxy-3-oxo-2-methoxyiminobutyryl-amino)cephalosporanic acid

(4) 7-(4-p-Toluenesulfonyloxy-3-oxo-2-methoxyiminobutyryl-amino)-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid

(5) 7-(4-p-Toluenesulfonyloxy-3-oxo-2-methoxyiminobutyryl-amino)-3-(4-methyl-5-oxo-6-hydroxy-4,5-dihydro-1,2,4-triazin-3-yl)thiomethyl-3-cephem-4-carboxylic acid

(6) 7-(4-p-Toluenesulfonyloxy-3-oxo-2-methoxyiminobutyryl-amino)-3-methoxymethyl-3-cephem-4-carboxylic acid

(7) 7-(4-Methanesulfonyloxy-3-oxo-2-methoxyiminobutyryl-amino)cephalosporanic acid

(8) 7-(4-Phenylsulfonyloxy-3-oxo-2-methoxyiminobutyryl-amino)-3-(2-methyl-1,3,4-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid

(9) Pivaloyloxymethyl 7-(4-p-toluenesulfonyloxy-3-oxo-2-methoxyiminobutyrylamino)-3-methyl-3-cephem-4-carboxylate

(10) Pivaloyloxymethyl 7-(4-p-toluenesulfonyloxy-3-oxo-2-methoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

(11) Pivaloyloxymethyl 7-(4-p-toluenesulfonyloxy -3-oxo-2-methoxyiminobutyrylamino)-3-cephem-4-carboxylate

(12) Benzhydryl 7-(4-p-toluenesulfonyloxy -3-oxo-2-methoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

(13) Methoxymethyl 7-(4-p-toluenesulfonyloxy -3-oxo-2-ethoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

(14) Benzyl 7-(4-p-toluenesulfonyloxy -3-oxo-2-methoxyiminobutyrylamino)-3-carbamoyloxymethyl-3-cephem-4-carboxylate

Compounds (II) obtained by the process of the invention will be illustrated below, in which they all take the syn-form.

(1) 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid

(2) 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid

(3) 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-cephalosporanic acid

(4) 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid

(5) 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-

3-methoxymethyl-3-cephem-4-carboxylic acid

(6) 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(4-methyl-5-oxo-6-hydroxy-4,5-dihydro-1,2,4-triazin-3-yl)thiomethyl-3-cephem-4-carboxylic acid

(7) Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

(8) Benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

(9) Isobutyryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

(10) 1-Ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

(11) Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

(12) Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-ethoxymethyl-3-cephem-4-carboxylate.

The process for preparing the compounds according to the present invention will be concretely explained by the following Referential Examples and Examples, which by no means restrict the scope of the inventions.

Referential Example 1

To 50 mℓ of dry acetonitrile were added 7.1 g of t-butyl 4-bromo-3-oxobutyrate and 9.45 g of silver p-toluenesulfonate, and the mixture was stirred for 3 days at room temperature under shielding of light. The reaction mixture was filtered and the filtrate was concentrated in vacuo.

Crystals containing an oily substance were dissolved in ethyl acetate, and the insolubles were removed by filtration. The filtrate was concentrated in vacuo to give a brown, oily substance, which was purified by column chromatography through silica gel, eluted with a mixture of cyclohexane and ethyl acetate. A colorless oily substance thus obtained was recrystallized from a mixture of ether and n-hexane to afford 4.5 g of t-butyl 4-p-toluenesulfonyloxy-3-oxobutyrate in the form of colorless prisms melting at 67 - 69 °C.

NMR ($CDC\ell_3$) δ ppm:

1.43 (9H, s, tert-butyl)

2.43 (3H, s, CH_3- )

3.43 (2H, s, $-CH_2COO$-t-Bu)

4.60 (2H, s, $-SO_2OCH_2CO-$)

7.20 - 7.90 (4H, benzene ring)

Elementary analysis for $C_{15}H_{20}O_6S$

Calcd.: C, 54.92; H, 6.15; S, 9.78

Found : C, 55.03; H, 6.07; S, 9.86

Referential Example 2

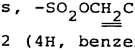
In 40 mℓ of acetic acid were dissolved 4.5 g of t-butyl 4-p-toluenesulfonyloxy-3-oxobutyrate, then 1.42 g of sodium nitrite were added at room temperature to the solution over 10 minutes.

After stirring for 50 minutes at room temperature, 200 mℓ of ethyl acetate were added to the reaction mixture, which was then washed with an aqueous sodium chloride solution. The ethyl acetate solution was dried over magnesium sulfate and concentrated to give a brown, oily substance, which was purified by column chromatography through silica gel, eluted with a mixture of cyclohexane and ethyl acetate, affording 1.66 g of t-butyl 4-p-toluenesulfonyloxy-3-oxo-2-hydroxyiminobutyrate in the form of colorless crystals. m.p. 106 - 108 °C (decomposition; recrystallized from a mixture of ether and petroleum ether).

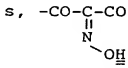
NMR ($CDCl_3$) δ ppm:

1.52 (9H, s, tert-butyl)

2.43 (3H, s, )

5.04 (2H, s, )

7.20 - 7.92 (4H, benzene ring)

10.23 (1H, s, )

Elementary analysis for $C_{15}H_{19}NO_7S$

Calcd.: C, 50.48; H, 5.36; N, 3.92; S, 8.98

Found : C, 50.62; H, 5.08; N, 3.83; S, 8.97

Referential Example 3

To an ice-cooled solution of 1.66 g of t-butyl 4-p-toluenesulfonyloxy-3-oxo-2-hydroxyiminobutyrate in 20 mℓ of dry acetone were added 960 mg of anhydrous potassium carbonate and 0.466 mℓ of dimethylsulfate, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into ice-water and extracted with methylene chloride. The extract was washed with an aqueous sodium chloride solution, dried over magnesium sulfate and concentrated to give a brown, oily substance.

This was purified by column chromatography through silica gel, eluted with a mixture of cyclohexane and ethyl acetate, affording 650 mg of t-butyl 4-p-toluenesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrate into form of a pale yellow oily substance.

NMR ($CDCℓ_3$) δ ppm:

1.50 (9H, s, tert-butyl)

2.43 (3H, s, $\underline{CH_3}$-⟨○⟩-)

4.07 (3H, s, $\underset{\underset{\underset{\underline{OCH_3}}{}}{N}}{\overset{\|}{}}$)

5.05 (2H, s, $-SO_2O\underline{CH_2}CO-$)

7.20 - 7.90 (benzene ring)

Referential Example 4

To a solution of 478 mg of t-butyl 4-p-toluenesulfonyl-oxy-3-oxo-2-(syn)methoxyiminobutyrate in 1 mℓ of methylene chloride were added 2 mℓ of trifluoroacetic acid, and the mixture was stirred at room temperature for 4 hours. The methylene chloride and the excess trifluoroacetic acid was distilled off in vacuo to give a brown, oily substance, which was dissolved in diisopropyl ether and allowed to stand, affording 178 mg of 4-p-toluenesulfonyloxy-3-oxo-2-(syn)-methoxyiminobutyric acid in the form of colorless crystals. m.p. 131 - 132 °C (decomposition).

Elementary analysis for $C_{12}H_{13}NO_7S$

Calcd.: C, 45.72; H, 3.84; N, 4.45; S, 10.18

Found : C, 45.50; H, 3.92; N, 4.32; S, 9.98

NMR (d-6 acetone) δ ppm:

2.47 (3H, s, $\underline{CH_3}$-⟨○⟩-)

4.10 (3H, s, $\underset{\underset{\underline{OCH_3}}{|}}{\overset{\|}{N}}$)

5.20 (2H, s, $-SO_2O\underline{CH_2}CO$)

7.25 - 7.95 (4H, benzene ring)

9.80 (1H, b.s, $-CO_2\underline{H}$)

Example 1

To a suspension of 464 mg of 4-p-toluenesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyric acid in 20 mℓ of methylene chloride cooled at -5 °C was added 0.204 mℓ of triethylamine,

and the mixture was stirred for 5 minutes, after which the resulting mixture became a solution. To the solution were added 0.17 mℓ of oxalyl chloride and a drop of dimethylformamide, and the mixture was stirred at -5 °C for 20 minutes. By removing the solvent, there was obtained 4-p-toluenesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyryl chloride. Then, 0.394 mℓ of diethylaniline and a solution of the above-obtained acid chloride in 10 mℓ of methylene chloride were added, in turn, at -5 °C to a solution of 530 mg of pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulfonic acid salt in 20 mℓ of methylene chloride. The mixture was stirred at -5 °C for 5 minutes and the solvent was distilled off. The resulting residue was dissolved in ethyl acetate and washed with a dilute aqueous hydrochloric acid. The ethyl acetate layer was dried over magnesium sulfate and concentrated to give a brown, oily substance. This was purified by column chromatography through silica gel, eluted with a mixture of cyclohexane and ethyl acetate to afford 510 mg of pivaloyloxymethyl 7-(4-p-toluenesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrylamino-3-methoxymethyl-3-cephem-4-carboxylate in the form of a colorless foamy substance.

NMR ($CDCl_3$) δ ppm:

1.22 (9H, s, tert-butyl)

2.43 (3H, s, CH_3--)

3.30 (3H, s, $-OCH_3$ at 3-position)

3.51 (2H, s, $-CH_2-$ at 2-position)

4.10 (3H, s, $\overset{\overset{\|}{N}}{\diagdown}OCH_3$)

4.27 (2H, s, $-CH_2-$ at 3-position)

4.97 (1H, d, J = 5.0, -H at 6-position)

5.07 (2H, s, $-SO_2OCH_2CO-$)

5.53 - 5.97 (3H, m, -H at 7-position and $-OCH_2O-$ of ester)

7.20 - 7.93 (5H, m, -NH- at 7-position and bezene ring).

Example 2

A solution of 4-p-toluenesulfonyloxy-3-oxo-2-(syn)-methoxyiminobutyryl chloride prepared by the method of Example 1 in 10 mℓ of methylene chloride was added to a solution cooled at -5 °C of 450 mg of pivaloyloxymethyl 7-amino-3-methyl-3-cephem-4-carboxylate hydrochloride and 0.4 mℓ of diethylaniline in 20 mℓ of methylene chloride. After stirring at room temperature for 15 minutes, the reaction mixture was washed with a dilute aqueous hydrochloric acid, dried over magnesium sulfate and concentrated. The residue was purified by column chromatography through silica gel to give 430 mg of pivaloyloxymethyl 7-(4-p-toluene-sulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrylamino)-3-methyl-

3-cephem-4-carboxylate in the form of a pale yellow powder.

NMR ($CDCl_3$) δ ppm:

1.23 (9H, s)

2.16 (3H, s)

2.44 (3H, s)

3.46 (2H, br)

4.09 (3H, s)

4.97 (1H, d)

5.07 (2H, s)

5.5 - 6.0 (3H, m)

7.2 - 7.9 (5H, m).

Example 3

A solution of 4-p-toluenesulfonyloxy-3-oxo-2-(syn)-methoxyiminobutyryl chloride prepared by the method of Example 1 in 10 mℓ of methylene chloride was added dropwise at -5 °C to a solution of 380 mg of 7-aminocephalosporanic acid and 1 g of bistrimethylsilylacetamide in 5 mℓ of ethyl acetate. After stirring for an hour under ice-cooling, 50 mℓ of ethyl acetate were added to the reaction mixture, which was concentrated in vacuo to about half the volume. The residue was washed, in turn, with water and an aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated. Ether was added to the precipitate, which was collected by filtrations to afford 420 mg of 7-(4-p-toluene-

sulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrylamino)cephalosporanic acid.

NMR (DMSO-d_6) δ ppm:

2.00 (3H, s)

2.49 (3H, s)

3.55 (2H, brs)

4.15 (3H, s)

4.85 (2H, q)

5.05 (1H, d)

5.10 (2H, s)

5.82 (1H, d.d)

7.2 - 7.8 (4H, brs)

Example 4

Following the procedures of Example 3, but using 350 mg of 7-amino-3-cephem-4-carboxylic acid in place of the 7-aminocephalosporanic acid, there were obtained 360 mg of 7-(4-p-toluenesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrylamino)-3-cephem-4-carboxylic acid.

NMR (DMSO-d_6) δ ppm:

2.42 (3H, s)

3.51 (2H, d)

4.12 (3H, s)

4.99 (1H, d)

5.10 (2H, s)

5.60 (1H, d.d)

6.51 (1H, s)

7.1 - 8.0 (4H, br.s)

Example 5

A solution of 4-p-toluenesulfonyloxy-3-oxo-2-(syn)-methoxyiminobutyryl chloride prepared by the method of Example 1 in 10 mℓ of methylene chloride was added dropwise to a solution cooled at -5 °C of 360 mg of benzhydryl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate and 300 mg of diethylaniline in 5 mℓ of methylene chloride. After stirring for 30 minutes under ice-cooling, the reaction mixture was washed, in turn, with a dilute aqueous hydrochloric acid and aqueous sodium chloride solution, and dried over magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography through silica gel to afford 420 mg of benzhydryl 7-(4-p-toluenesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate.

NMR ($CDCℓ_3$) δ ppm:

2.43 (3H, s)

3.30 (3H, s)

3.53 (2H, s)

4.08 (3H, s)

4.29 (2H, q)

5.00 (1H, d)

5.09 (2H, s)

5.65 (1H, d.d)

6.90 (1H, s)

7.2 - 7.8 (14H, br.s)

Example 6

To a solution of 510 mg of pivaloyloxymethyl 7-(4-p-toluenesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate in 5 mℓ of ethanol were added 76 mg of thiourea and 84 mg of sodium acetate. To the mixture were added 3 mℓ of water, little by little, and the whole mixture was stirred at room temperature for 3.5 hours. The ethanol was removed by distillation and the residue was dissolved in ethyl acetate, washed with an aqueous sodium hydrochloride solution, and dried over magnesium sulfate. By concentration of the ethyl acetate layer, there was obtained a pale brown, foamy substance, which was purified by column chromatography through silica gel, affording 392 mg of pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-(syn)methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate in the form of a colorless, foamy substance.

NMR ($CDCℓ_3$) δ ppm:

1.22 (9H, s, t-butyl)

3.30 (3H, s, $-OCH_3$)

3.53 (2H, s, $-\underline{\underline{CH_2}}$ at 2-position)

4.00 (3H, s, $\underset{\underset{\underline{\underline{OCH_3}}}{|}}{\overset{\overset{||}{N}}{}}$)

4.30 (2H, s, $-\underline{\underline{CH_2}}-$ at 3-position)

5.05 (1H, d, J = 5.0, $-\underline{H}$ at 6-position)

5.70 - 6.30 (5H, m, $-\underline{H}$ at 7-position, $-\underline{\underline{NH_2}}$ of lateral chain, and $-\underline{\underline{OCH_2}}O-$ of ester)

6.63 (1H, s, $-\underline{H}$ at 5-position of aminothiazole ring)

8.27 (1H, d, J = 9.0, $-N\underline{H}$ at 7-position).

Example 7

Following the procedures of Example 6 and using 490 mg of propionyloxymethyl 7-(4-p-toluenesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate, there were obtained 370 mg of propionyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-(syn)methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate.

NMR ($CDCl_3$) δ ppm:

1.17 (3H, t)

2.41 (2H, q)

3.28 (3H, s)

3.51 (2H, q)

4.02 (3H, s)

4.27 (2H, s)

5.08 (1H, d)

5.6 - 6.2 (5H, m)

6.67 (1H, s)

8.10 (1H, d)

Example 8

Following the procedures of Example 6, there were obtained the following compounds.

A) 1-Ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

NMR ($CDCl_3$) δ ppm:

1.30 (3H, t)

1.61 (3H, d)

3.32 (3H, s)

3.57 (2H, s)

4.03 (3H, s)

4.21 (2H, q)

4.30 (2H, s)

5.10 (1H, d)

5.6 - 6.2 (3H, m)

6.70 (1H, s)

6.92 (1H, q)

8.20 (1H, d)

B) Isobutyryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

NMR ($CDCl_3$) δ ppm:

1.20 (6H, d)

2.66 (1H, septet)

3.21 (3H, s)

3.40 (2H, q)

4.01 (3H, s)

4.16 (2H, s)

5.05 (1H, d)

5.6 - 6.2 (5H, m)

6.65 (1H, s)

8.06 (1H, d)

C) Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-ethoxymethyl-3-cephem-4-carboxylate

NMR ($CDCl_3$) δ ppm:

1.19 (3H, t)

1.24 (9H, s)

3.49 (2H, q)

3.58 (2H, s)

4.06 (3H, s)

4.37 (2H, s)

5.07 (1H, d)

5.57 (2H, s)

5.88 (2H, s)

6.04 (1H, d.d)

6.76 (1H, s)

7.90 (1H, d)

D) Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

NMR ($CDCl_3$) δ ppm:

1.22 (9H, s)

1.31 (3H, t)

3.30 (3H, s)

3.53 (2H, s)

4.28 (2H, s)

4.38 (2H, q)

5.01 (1H, d)

5.7 - 6.2 (5H, m)

6.71 (1H, s)

8.28 (1H, d)

Example 9

To a solution of 350 mg of 7-(4-p-toluenesulfonyloxy-3-oxo-2-methoxyiminobutyrylamino)-3-(1-methyl-1H-tetrazol-5-yl)-thiomethyl-3-cephem-4-carboxylic acid in 5 mℓ of dimethylacetamide were added 100 mg of thiourea, and the mixture was stirred at room temperature for 4 hours. 50 mℓ of ether were added to the reaction mixture and insolubles precipitated were separated, dissolved in a small amount of a 5% aqueous sodium bicarbonate solution and purified by column chromatography through Amberlite XAD-2, affording 160 mg of sodium 7-[2-(2-aminothiazol-4-yl)-2-(syn)methoxyiminoacetamido-3-

(1-methyl-1H-tetrazol-4-yl)thiomethyl-3-cephem-4-carboxylate in the form of a colorless powder. Yield, 160 mg.

NMR (D_2O) δ ppm:

3.59 (2H, q)

3.93 (3H, s)

3.99 (3H, s)

4.10 (2H, q)

5.11 (1H, d)

5.72 (1H, d)

6.95 (1H, s)

Example 10

Following the procedures of Example 9 and using 300 mg of 7-(4-p-toluenesulfonyloxyiminobutyrylamino)cephalosporanic acid, there were obtained 140 mg of sodium 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporanate.

NMR (D_2O) δ ppm:

2.10 (3H, s)

3.53 (2H, q)

3.98 (3H, s)

4.75 (2H, q)

5.21 (1H, d)

5.81 (1H, d)

7.00 (1H, s)

Example 11

A mixture of 600 mg of 7-(4-p-toluenesulfonyloxy-3-oxo-2-methoxyiminobutyrylamino)-3-cephem-4-carboxylic acid, 200 mg of thiourea, 150 mg of sodium acetate and 5 mℓ of methanol was stirred at room temperature for 5 hours. To the reaction mixture were added 20 mℓ of diisopropyl ether and the resulting precipitate was collected by filtration and washed with ether. There were thus obtained 400 mg of 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid (syn-isomer).

NMR (D_2O) δ ppm:

3.60 (2H, m)

3.98 (3H, s)

5.16 (1H, d)

5.80 (1H, d)

6.30 (1H, t)

6.98 (1H, s)

Example 12

Following the procedures of Example 11 and using 650 mg of 7-(4-p-toluenesulfonyloxy-3-oxo-2-methoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylic acid, there were obtained 360 mg of 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido-3-methoxymethyl-3-cephem-4-carboxylic acid. This was added to 3 mℓ of methanol, and 1 mℓ of sodium 2-ethylhexanoate in ethyl acetate (2M) was added thereto to make a solution. The

solvent was partly removed by distillation and crystals separated were collected by filtration, using ethyl acetate, and washed with ethyl acetate to afford 350 mg of sodium salt of the above carboxylic acid.

NMR (DMSO-D_2O) δ ppm:

3.18 (3H, s)

3.34 (2H, br)

3.87 (3H, s)

4.25 (2H, s)

5.00 (1H, d)

5.59 (1H, d.d)

6.74 (1H, s)

7.26 (2H, br)

9.52 (1H, d)

Example 13

Following the procedures of Example 11 and using the corresponding compound (I) and thiourea, there were obtained the following compounds.

A) 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(4-methyl-5-oxo-6-hydroxy-4,5-dihydro-1,2,4-triazin-3-yl)-thiomethyl-3-cephem-4-carboxylic acid

NMR (DMSO-d_6) δ ppm:

3.30 (3H, s)

3.63 (2H, s)

3.93 (3H, s)

4.12 (1H, q)

5.13 (1H, d)

5.79 (1H, q)

6.73 (1H, s)

7.21 (2H, s)

9.59 (1H, d)

B) 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(2-methyl-5-oxo-6-hydroxy-2,5-dihydro-1,2,4-triazin-3-yl)-thiomethyl-3-cephem-4-carboxylic acid

NMR (DMSO-d_6) δ ppm:

3.58 (2H, br)

3.61 (3H, s)

3.91 (3H, s)

4.18 (2H, q)

5.12 (1H, d)

5.77 (1H, d.d)

6.88 (1H, s)

7.21 (2H, s)

9.53 (1H, d)

Patent Applicant : Sankyo Company, Limited

Agent, Patent Attorney : Shoji Kashiide

Written Supplement of Proceedings (Voluntary)

July 3, 1981

To : Haruki Shimada, Director-General of the Patent Office

1. Indication of the case

Patent Application No. 55231/1981

2. Title of the invention

Cephalosporin derivatives and preparation therof

3. Person making the supplement

Relation with the case Patent Applicant

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Name Patent Attorney (6007) Shoji Kashiide (Seal)

5. Number of invention to be increased by supplement: 1

6. Subject matter to be supplemented

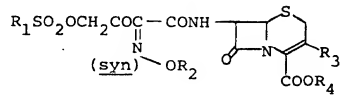
Scope of patent claim and Detailed explanation of the invention in the specification

7. Contents of supplement

As given in the annexed paper

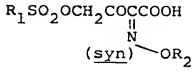
1. Amend the Scope of patent claim as follows.

"(1) A cephalosporin derivative having the general formula



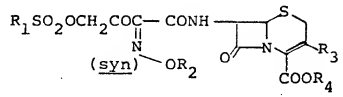
[wherein, R_1 represents an optionally substituted phenyl group, or a lower alkyl group; R_2 represents a lower alkyl group; R_3 represents a hydrogen atom, a halogen atom, a hydroxy group, a lower alkoxy group or a group of formula $-CH_2R_5$ (in which R_5 represents a hydrogen atom, a hydroxy group, a lower alkoxy group, a halogen atom, an azido group, an acyloxy group, a carbamoyloxy group or an optionally substituted heterocyclicthio group); and $COOR_4$ represents an optionally esterified carboxyl group].

(2) An alkoxyiminobutyric acid derivative having the general formula



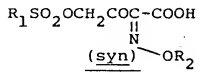
[wherein, R_1 represents an optionally substituted phenyl group, or a lower alkyl group; and R_2 represents a lower alkyl group].

(3) A process for preparing cephalosporin derivatives having the general formula



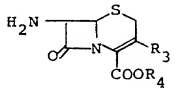
[wherein, R_1 represents an optionally substituted phenyl group, or a lower alkyl group; R_2 represents a lower alkyl group; R_3 represents a hydrogen atom, a halogen atom, a hydroxy group, a lower alkoxy group or a group of formula $-CH_2R_5$ (in which R_5 represents a hydrogen atom, a hydroxy group, a lower alkoxy group, a halogen atom, an azido group, an acyloxy group, a carbamoyloxy group or an optionally substituted heterocyclicthio group); and $COOR_4$ represents an optionally esterified carboxyl group]

which comprises reacting an alkoxyiminobutyric acid having the general formula



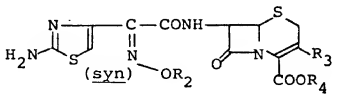
(wherein, R_1 and R_2 are as defined above)

or a reactive derivative thereof at the carboxyl group with an 7-aminocephalosporin derivative having the general formula



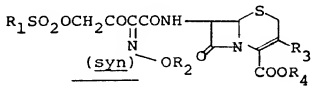
(wherein, R_3 and $COOR_4$ are as defined above).

(4) A process for preparing cephalosporin derivatives having the general formula



[wherein, R_2 represents a lower alkyl group; R_3 represents a hydrogen atom, a halogen atom, a hydroxy group, a lower alkoxy group or a group of formula $-CH_2R_5$ (in which R_5 represents a hydrogen atom, a hydroxy group, a lower alkoxy group, a halogen atom, an azido group, an acyloxy group, a carbamoyloxy group or an optionally substituted heterocyclicthio group); and $COOR_4$ represents an optionally esterified carboxyl group]

which comprises reacting a compound having the general formula

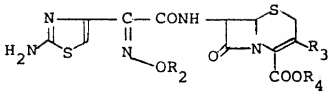


[wherein, R_1 represents an optionally substituted phenyl group, or a lower alkyl group; and R_2, R_3 and $COOR_4$ are as defined above]

with thiourea.

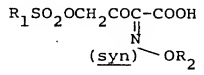
(5) A process for preparing cepharosporin derivatives having

the general formula



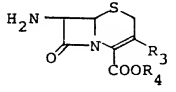
[wherein, R_2 represents a lower alkyl group; R_3 represents a hydrogen atom, a halogen atom, a hydroxy group, a lower alkoxy group or a group of formula $-CH_2R_5$ (in which R_5 represents a hydrogen atom, a hydroxy group, a lower alkoxy group, a halogen atom, an azido group, an acyloxy group, a carbamoyloxy group or an optionally substituted heterocyclicthio group); and $COOR_4$ represents an optionally esterified carboxyl group]

which comprises reacting an alkoxyiminobutyric acid having the general formula

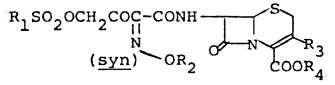


[wherein, R_1 represents an optionally substituted phenyl group, or a lower alkyl group; and R_2 is as defined above]

or a reactive derivative thereof at the carboxyl group with an 7-aminocephalosporin derivative having the general formula



(wherein, R_3 and $COOR_4$ are as defined above)
to give a compound having the general formula



(wherein, R_1, R_2, R_3 and $COOR_4$ are as defined above), and reacting the compound with thiourea".

2. Specification at page 18, line 11; amend "(8) 7-(4-phenylsulfonyloxy-" to read "(8) 7-(4-benzenesulfonyloxy-".

3. Specification at page 20, after "3-cephem-4-carboxylic acid benzyl ester" at lines 3 and 4, insert the following:

"(15) Pivaloyloxymethyl 7-(4-ethanesulfonyloxy-3-oxo-2-methoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

(16) Pivaloyloxymethyl 7-(4-benzenesulfonyloxy-3-oxo-2-methoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate".

4. Specification at page 35, line 13; amend "4.00 (3H, s, $\overset{\|}{N}$-OCH_2)" to read "4.00, s, $\overset{\|}{N}$-OCH_3)".

5. Specification at page 40, lines 8 and 9; amend

"4.28 (2H, s)

4.38 (2H, q)"

to read

"4.28 (2H, q)

4.30 (2H, s)".

6. Specification at page 40, lines 12 and 13; amend

"6.71 (1H, s)

8.28 (1H, d)"

to read

"6.76 (1H, s)

7.70 (1H, d)".

7. Specification, after the description of "Referential Example 4" at page 27, line 14, insert the following:

"Referential Example 5

To 50 mℓ of dry acetonitrile were added 8.25 g of t-butyl 4-bromo-3-oxobutyrate and 11.3 g of silver ethanesulfonate, and the mixture was refluxed, under stirring, for 30 minutes.

The reaction mixture was filtered and the filtrate was concentrated in vacuo. The oily product thus obtained was dissolved in benzene, washed, in turn, with water, an aqueous sodium bicarbonate solution and an aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. By removing the solvent, there was obtained a brown, oily substance, which was purified by column chromatography through silica gel, eluted with a mixture of cyclohexane and ethyl acetate, affording 7.7 g of t-butyl 4-ethanesulfonyloxy-3-oxobutyrate

in the form of a yellow oil.

NMR ($CDC\ell_3$) δ ppm:

1.32 - 1.62 (9H + 3H, s + t, tert-butyl + $\underline{CH_3}CH_2SO_3$-)

3.30 (2H, q, J = 7.0, $CH_3\underline{CH_2}SO_3$-)

3.47 (2H, s, $-\underline{CH_2}CO_2$-t-Bu)

4.87 (2H, s, $-SO_2\underline{CH_2}CO$-)

Referential Example 6

To a solution of 7.7 g of t-butyl 4-ethanesulfonyloxy-3-oxobutyrate in 50 mℓ of acetic acid were added, under ice-cooling, 2.2 g of sodium nitrite and 0.1 mℓ of conc. sulfuric acid. The reaction mixture was stirred at room temperature for 40 minutes, then diluted with 500 mℓ of ethyl acetate.

The ethyl acetate solution was washed with an aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated to give yellowish brown crystals.

The crystals were recrystallized from a mixture of ether and petroleum ether, affording 5.9 g of t-butyl 4-ethanesulfonyloxy-3-oxo-2-hydroxyiminobutyrate in the form of colorless crystals.

m.p. 85 - 87 °C (decomposition)

NMR ($CDC\ell_3$) δ ppm:

1.47 (3H, t, J = 7.0, $\underline{CH_3}CH_2SO_2O$-)

1.57 (9H, s, t-butyl)

3.33 (2H, q, J = 7.0, $CH_3\underline{CH_2}SO_2O$-)

5.23 (2H, s, $-SO_2OCH_2CO-$)

10.50 (1H, s, $-COC(=N-OH)CO-$)

Elementary analysis for $C_{10}H_{17}NO_7S$

Calcd.: C, 40.71; H, 5.81; N, 4.75; S, 10.87

Found : C, 40.29; H, 5.73; N, 4.61; S, 11.17

Referential Example 7

To a solution of 5.9 g of t-butyl 4-ethanesulfonyloxy-3-oxo-2-hydroxyiminobutyrate in 50 mℓ of dry acetone were dissolved, under ice-cooling, 4.14 g of anhydrous potassium carbonate and 1.86 mℓ of dimethyl sulfate, and the mixture was stirred at room temperature for an hour. The reaction mixture was poured into 500 mℓ of ice-water and extracted with ethyl acetate. The extract was washed with an aqueous sodium chloride solution, dried over magnesium sulfate and concentrated to give a brown, oily substance. This was purified by column chromatography through silica gel, eluted with a mixture of benzene and ethyl acetate, affording 3.13 g of t-butyl 4-ethanesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrate in the form of a pale yellow oil.

NMR ($CDCℓ_3$) δ ppm:

1.43 (3H, t, J = 7.0, $CH_3CH_2SO_2O-$)

1.50 (9H, s, t-butyl)

3.27 (2H, q, J = 7.0, $CH_3CH_2SO_2O-$)

4.07 (3H, s, -COC(=N-OCH$_3$)CO-)

5.18 (2H, s, -SO$_2$OCH$_2$CO-)

Referential Example 8

Following the procedures of Example 5 and using 5.0 g of t-butyl 4-bromo-3-oxobutyrate and 6.5 g of silver benzenesulfonate, there were obtained 3.4 g of t-butyl 4-benzenesulfonyloxy-3-oxobutyrate in the form of colorless needles.

m.p. 94 - 96 °C

Elementary analysis for $C_{14}H_{18}O_6S$

Calcd.: C, 53.50; H, 5.78; S, 10.20

Found : C, 53.49; H, 5.70; S, 10.16

NMR ($CDCl_3$) δ ppm

1.43 (9H, s, t-butyl)

3.43 (2H, s, -COCH$_2$CO-)

4.63 (2H, s, -SO$_2$OCH$_2$CO-)

7.40 - 8.03 (5H, m, H in benzene ring)

Referential Example 9

Following the procedures of Referential Example 2 and using 3.4 g of t-butyl 4-benzene sulfonyloxy-3-oxobutyrate and 900 mg of sodium nitrite, there were obtained 2.95 g of t-butyl 4-benzenesulfonyloxy-3-oxo-2-hydroxyiminobutyrate in the form of colorless needles.

m.p. 93 - 95 °C (decomposition)

Elementary analysis for $C_{14}H_{17}NO_7S$

Calcd.: C, 49.02; H, 5.00; N, 4.08; S, 9.35

Found : C, 48.93; H, 5.06; N, 4.01; S, 9.41

NMR ($CDCl_3$) δ ppm:

1.57 (9H, s, t-butyl)

5.07 (2H, s, $-SO_2OCH_2CO-$)

7.40 - 8.03 (5H, m, H in benzene ring)

10.17 (1H, b.s, $\overset{\overset{\|}{N}}{}-OH$)

Referential Example 10

Following the procedures of Referential Example 3 and using 2.95 g of t-butyl 4-benzenesulfonyloxy-3-oxo-2-hydroxyiminobutyrate, 1.80 g of anhydrous potassium carbonate and 0.8 mℓ of dimethyl sulfate, there were obtained 800 mg of t-butyl 4-benzenesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrate in the form of a colorless oil.

NMR ($CDCl_3$) δ ppm:

1.50 (9H, s, t-butyl)

4.05 (3H, s, $\overset{\overset{\|}{N}}{}-OCH_3$)

5.07 (2H, s, $-SO_2OCH_2CO-$)

7.30 - 8.00 (5H, m, H in benzene ring)".

8. Specification, after the description of Example 13" at page 46, line 12, insert the following:

"Example 14

A solution of 1.56 g of t-butyl 4-ethanesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrate in 5 mℓ of trifluoroacetic acid was stirred at room temperature for 7 hours. By concentrating the reaction mixture, there was obtained a brown oil, which was allowed to stand overnight, giving crystals.

The crystals were dissolved in acetone and treated with charcoal. The solution was concentrated and crystals precipitated were recrystallized from a mixture of methylene chloride and petroleum ether, affording 995 mg of 4-ethanesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyric acid.

m.p. 85.5 - 89 °C

NMR (deuteroacetone) δ ppm:

1.40 (3H, t, J = 7.0, $CH_3CH_2SO_2O$-)

3.34 (2H, q, J = 7.0, $CH_3CH_2SO_2O$-)

4.13 (3H, s, -COC(=N-OCH_3)-CO-)

5.33 (2H, s, $-SO_2OCH_2CO-$)

11.10 (1H, b.s, $-CO_2H$)

Elementary analysis

Calcd.: C, 33.23; H, 4.38; N, 5.54; S, 12.67

Found : C, 33.16; H, 4.29; N, 5.49; S, 12.67

Example 15

To a solution of 480 mg of 4-ethanesulfonyl-3-oxo-2-(syn)methoxyiminobutyric acid in 20 mℓ of methylene chloride

cooled at -5 °C, were added 0.263 mℓ of triethylamine, 0.22 mℓ of oxalyl chloride and a drop of dimethylformamide, and the mixture was stirred at -5 °C for 20 minutes. By removing the solvent by distillation, there was obtained 4-ethanesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyryl chloride.

On the other hand, 0.51 mℓ of diethylaniline was added, at -5 °C, to a solution of 690 mg of pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulfonic acid salt in 20 mℓ of methylene chloride, then the above-prepared acid chloride in 10 mℓ of methylene chloride was added. The mixture was stirred at -5 °C for 10 minutes and the solvent was distilled off. The residue was dissolved in ethyl acetate and washed, in turn, with a dilute aqueous hydrochloric acid and water, dried over magnesium sulfate and concentrated to give a brown, foamy substance.

This was purified by column chromatography through silica gel, eluted with a mixture of cyclohexane and ethyl acetate, affording 632 mg of pivaloyloxymethyl 7-(4-ethanesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate in the form of a colorless foam.

NMR ($CDCl_3$) δ ppm:

1.22 (9H, s, t-butyl)

1.43 (3H, t, J = 7.0, $CH_3CH_2SO_2O$-)

3.27 (2H, q, J = 7.0, $CH_3CH_2SO_2O$-)

3.30 (3H, s, $-OCH_3$ at 3-position)

3.54 (2H, b.s, $-CH_2-$ at 2-position)

4.13 (3H, s, $\overset{\overset{\|}{N}}{}-OCH_3$)

4.26 (2H, s, $-CH_2-$ at 3-position)

5.00 (1H, d, J = 5.0, H at 6-position)

5.27 (2H, s, $-SO_2OCH_2CO-$)

5.60 - 5.97 (3H, m, H at 7-position and $-OCH_2O-$ of ester)

7.55 (1H, d, J = 9.0, -NH- at 7-position)

Example 16

To a solution of 632 mg of pivaloyloxymethyl 7-(4-ethanesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate in 8 mℓ of ethanol were added 91 mg of thiourea and 146 mg of sodium acetate, then little by little 3 mℓ of water. The mixture was stirred at room temperature for 5.5 hours and the ethanol was distilled off. The residue was dissolved in ethyl acetate and washed with an aqueous sodium chloride solution. The solution was then dried over magnesium sulfate and concentrated to give a brown, foamy substance. This was purified by column chromatography through silica gel to afford 440 mg of pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-(syn)methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, which was identical with the product of Example 6, in the form of a colorless foam.

Example 17

Following the procedures of Example 14 and using 800 mg of t-butyl 4-benzenesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrate and 5 mℓ of trifluoroacetic acid, there were obtained 600 mg of 4-benzenesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyric acid in the form of crystals.

NMR (deuteroacetone) δ ppm:

4.06 (3H, s, $\overset{\|}{N}$-OCH$_3$)

5.17 (2H, s, -SO$_2$-O-CH$_2$-CO-)

7.37 - 8.03 (5H, m, H in benzene ring)

10.33 (1H, s, -CO$_2$H)

Example 18

Following the procedures of Example 1 and using 350 mg of 4-benzenesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyric acid and 530 mg of pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulfonic acid salt, there were obtained 510 mg of pivaloyloxymethyl 7-(4-benzenesulfonyloxy-3-oxo-2-(syn)methoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate in the form of a pale yellow foam.

NMR ($CDCl_3$) δ ppm:

1.22 (9H, s, t-butyl)

3.30 (3H, s, -OCH$_3$ at 3-position)

3.52 (2H, b.s, -CH$_2$- at 2-position)

4.10 (3H, s, $\overset{\|}{N}$-OCH$_3$)

4.27 (2H, s, $-\underline{CH_2}-$ at 3-position)

4.98 (1H, d, J = 5.0, H at 6-position)

5.08 (2H, s, $-SO_2OCH_2CO-$)

5.60 - 5.90 (3H, m, H at 7-position and $-OCH_2O-$ of ester)

7.40 - 8.03 (5H, m, H in benzene ring)

Example 19

Following the procedures of Example 6 and using 510 mg of pivaloyloxymethyl 7-(4-benzenesulfonyloxy-3-oxo-2-(syn)-methoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate and 76 mg of thiourea, there were obtained 360 mg of pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-(syn)methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate".